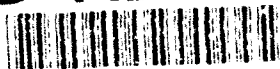


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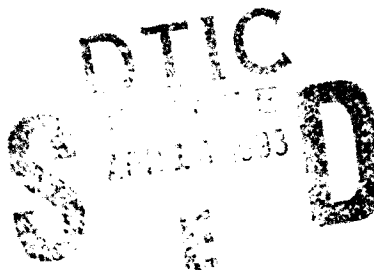


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Quarterly Progress Report Number 6

**Transcutaneous Analyte Measuring Methods
(TAMM Phase II)**

Dr. Kenneth J. Schlager



Biotronics Technologies, Inc.

January, February, March, 1993

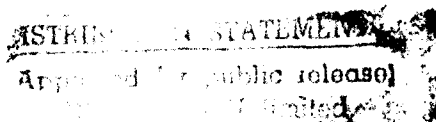
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Naval Medical Research and Development Command



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Transcutaneous Analyte Measuring Methods
(TAMM Phase II)

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Prepared by
Principal Investigator
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April 2, 1993

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Abstract

The major objective of this quarter was to complete all patient data collection at Froedtert Lutheran Memorial Hospital (Medical College of Wisconsin), finalize all TMM algorithms, integrate the new diagnostic software into the NIR-800 Array Analyzer and deliver the instrument to the Naval Health Research Center (NHRC) in San Diego, California. All of the above work activities were completed, and the NIR-800 was shipped to NHRC on March 9, 1993.

Prior to shipment, test set runs on all 9 of the analytes were completed with the results shown in Table 1. All of the electrolytes recorded average errors of less than 6% of mean value with all except bicarbonate less than 4%. The reliable operating range of the system for each analyte is also indicated in Table 1. This limited range results from the lack of sufficient extreme values for all analytes except glucose. Even glucose by these standards is marginal because only a few values over 150 mg/dl were obtained during preclinical testing. Extension of this range to include abnormal values for each analyte will require additional data collection in an Intensive Care Unit (ICU) where extreme analyte concentration values are common. Data on 531 patients have been collected of which 514 were acceptable. Best results were obtained using the final 73 patients for whom data collection instrumentation and procedures were optimized.

Project emphasis for the next quarter and the remainder of the Phase II contract ending in August of 1993 is on the development and delivery of the field instrument. A description of the preliminary field instrument design is included in this report.

Data Collection

Data collection was resumed on January 20 and continued until February 15. Two major changes were incorporated in the NIR-800 for this final series of preclinical tests:

1. Integration Time

The integration time on the self-scanned photodiode array was increased to 150 milliseconds and 250 milliseconds with each patient tested twice at each integration time. These times compared to integration times of 60 and 100 milliseconds used earlier (see Table 2).

2. Fixed Arm Position

The major source of noise in all of the earlier runs was isolated to probe movement by the operator. For the first time, the arm position of the patient was fixed on an arm rest with an accompanying strap. Noise levels were reduced by a factor of at least 4:1.

A summary of all 5 data subsets is shown in Table 2. The data sets differ in the experimental conditions of the various instrumentation parameters:

1. Probe position

- mobile or fixed

2. Integration time

- 60, 100, 150 or 250 milliseconds

3. Scan Sequence

- number of light and dark readings in each sequence

All three of these parameters were influential in improving instrument signal-to-noise ratio:

1. Probe position

The fixed probe position reduced the "noise" induced by probe movement characteristic of the mobile (hand-held) probe.

2. Integration time

Generally, the longer the integration time the better the signal-to-noise ratio. The limit is dark noise saturation.

3. Scan sequence

Early on in the program, a 10 light and 10 dark scan sequence was used. It was later found better to use a 90 light and 90 dark scan sequence, producing a less distorted signal pattern.

From Table 2 it can be seen that only data subset 5 included the optimal set of instrumentation parameters with a fixed probe position, integration times of 150/250 milliseconds and a 90/90 scan sequence. Although there are listed only 73 patient samples in data subset 5, there were actually 4 scans taken of each patient (2 at 150 milliseconds and 2 at 250 milliseconds) for a total of 292 patient spectra. These 292 spectra were used in various combinations to develop the algorithms discussed in the section that follows.

Algorithm Development

The genetic neural network software package NETGEN was used exclusively in all final algorithm development. NETGEN has proven superior to other pattern recognition techniques in previous analyses. Using the 292 patient spectra in data subset 5, a NETGEN neural network parameter set was generated that was used to produce the analyte concentration performance indicated in Table 1. The primary limitation of these algorithms is the lack of sufficient range of the analyte values. This lack of range is not a limitation of NETGEN but of the database itself. None of the subsets contained sufficient values in the abnormal high and low categories. Data subsets 1 and 2 collected at Bethesda contained virtually no abnormal values because they were collected from healthy members of the armed forces taking annual physicals. Data in the other three subsets were collected in an outpatient clinic, but with the exception of a few diabetics, most analyte concentration values were in the normal range.

Improvement in algorithm range must await the collection of data from at least 200 patients in ICU setting where abnormal analyte values are more common. While not a part of this SBIR Phase II contract, it is hoped that a joint effort involving Biotronics and the NHRC can accomplish this beginning in October of 1993.

NIR-800 Reconfiguration and Delivery

The NIR-800 Array Analyzer was originally designed as a data collection instrument to acquire near infrared (NIR) spectra to build a patient database for TAMM algorithm development. The instrument was composed of four primary components:

1. The light source module
2. The spectrometer module
3. The fiber bundle probe
4. The calibration module
 - for wavelength and light level calibration

The NIR-800 operated initially with software that supervised a series of 90 scans of NIR spectra of four separate body locations and also accepted other related patient information. This software allowed for variable integration times and scan sequences. It is also provided for matching laboratory test results with each patient record. In this configuration, all of the data were collected at Bethesda and Froedtert on individual diskettes - one for each patient.

Responding to the Navy's request, the NIR-800 was then reconfigured to operate as a diagnostic system in which a patient NIR scan would be converted in an estimate of concentration of the 9 chemical analytes. This reconfiguration required the development of a completely new software package including both analytical software for NETGEN implementation and a new, prompting user interface. Instrumentation changes for this reconfiguration were minor, but the software effort was of major proportions. A block diagram of the new diagnostic software is shown in figure 1. With the completion of the new software package, the NIR-800 was tested on a number of Biotronics employees and then shipped to the NHRC on March 9th. Plans call for a start-up and training session for NHRC personnel the first week of April.

Field Instrument Development

The final major work activity of this Phase II SBIR program is the development of the TAMM field instrument. The original target specifications of this instrument emphasized light weight and portability, so that it could be carried by paramedical personnel in a combat casualty situation. More specifically, the following four characteristics of the field instrument were emphasized in the Phase II proposal.

1. Flexibility
 - less flexible than the original NIR-800 particularly with a more restricted wavelength range.
2. Size and Weight
 - reduced to less than 20 pounds in weight.
 - note: the 20 pound requirement was not in the original Phase II proposal but has been adopted as a target requirement recently.
3. Battery-powered
 - This requirement was originally stated and has had a major influence on design decisions.
4. Self-Contained Integrated Operation
 - No PC-like microcomputer will be required.

The specifications for the current design of the TAMM Field Instrument are included in Appendix I. Some of the highlights of this design are:

1. Wavelength range 1150-1310 nm
2. Light source
 - An attempt is being made to use light emitting diodes as light sources.

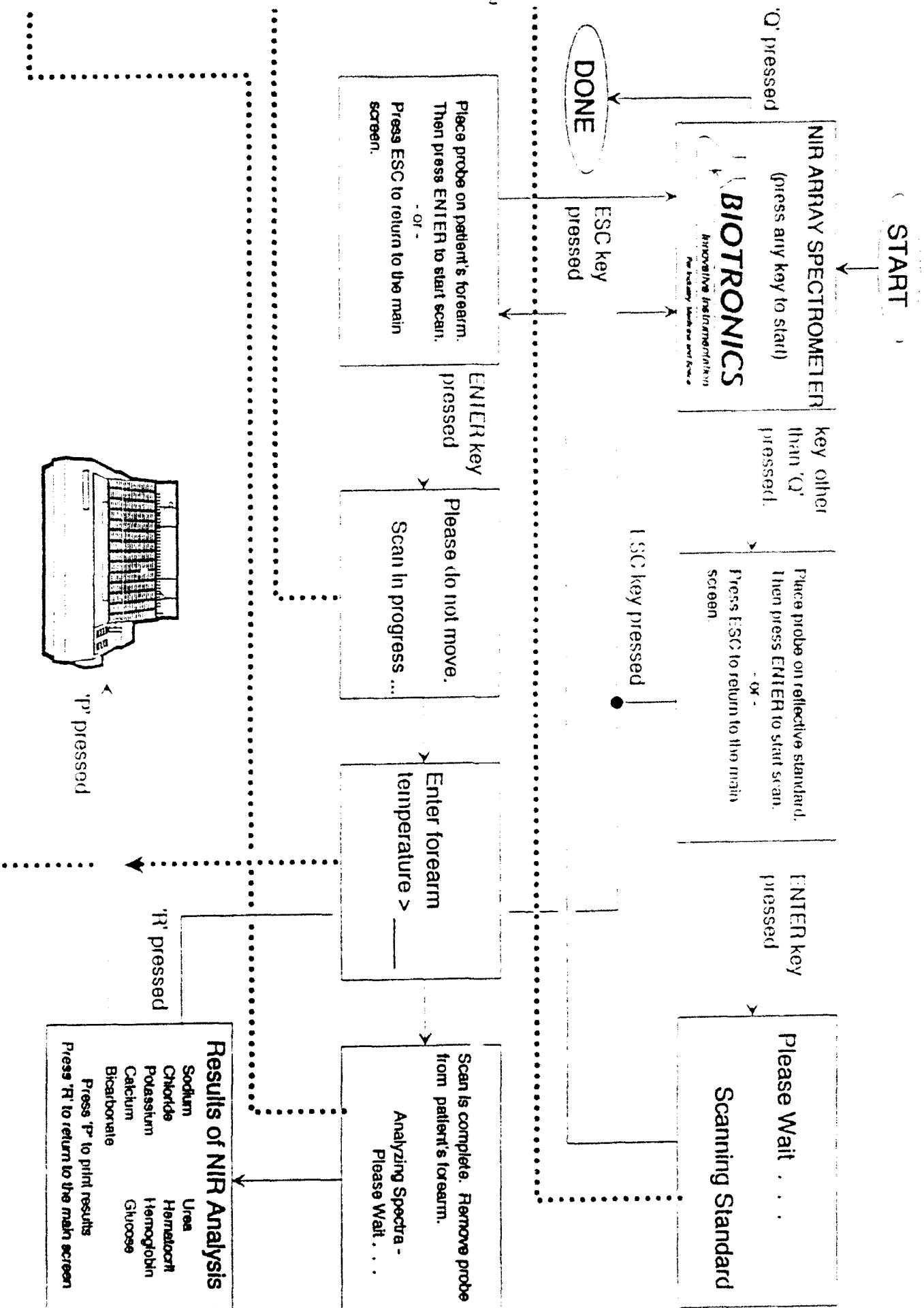


Figure 1

3. **Direct-readout Photodetector Array**

The smaller number of detectors needed allows for the direct readout approach with its better signal-noise performance.

4. **Direct Reflective (no fiber) measurements**

The fiber optical probe has been eliminated for both cost and rigidity reasons.

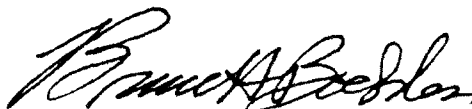
The field instrument promises to be not only a smaller and light-weight instrument but also a better performing instrument with a better signal-to-noise ratio.

Summary

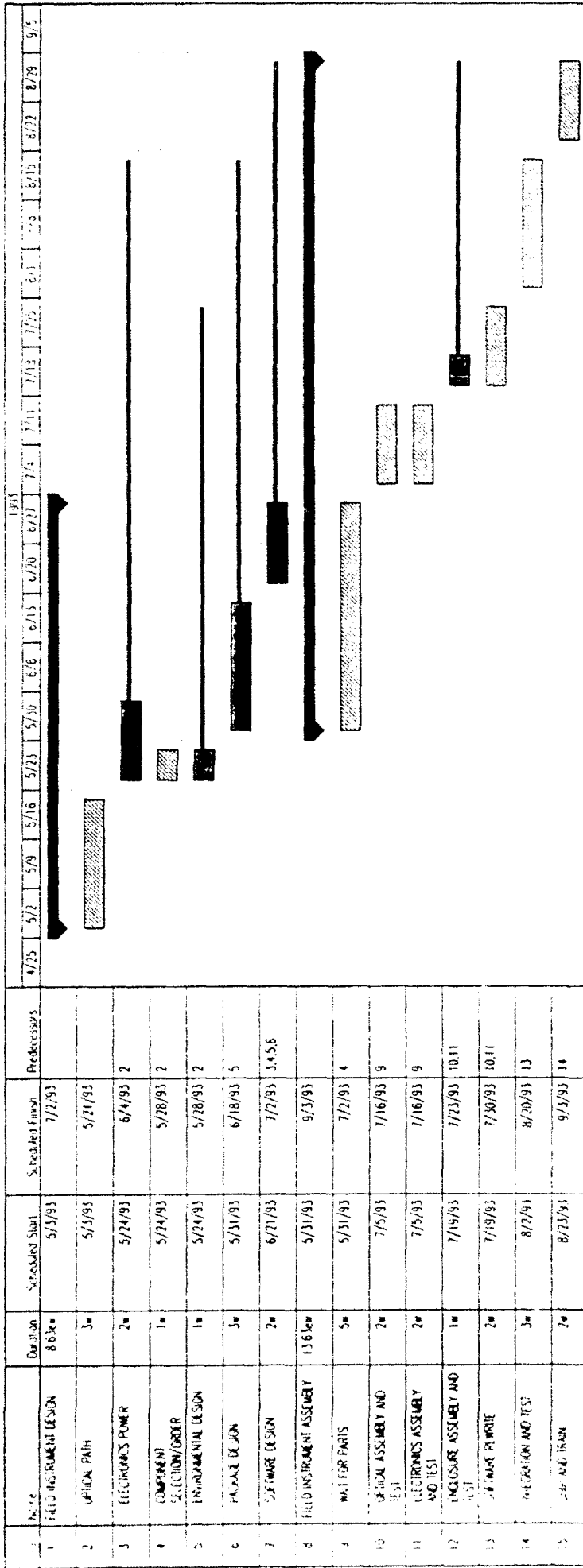
All work activities in the areas of pre-clinical data collection, data analysis and algorithm development have now been completed. The diagnostic version of the NIR-800 will be installed and training provided to NHRC personnel in early April. The only remaining task on this Phase II SBIR contract will be the development and delivery of the TAMM field instrument. A revised schedule calling for a August 23, 1993 shipment of the field instrument is shown in Figure 2.



Kenneth J. Schlager
Principal Investigator



Bruce H. Boehlen
Project Manager



Analyte	Mean Value	Range	Average Error	Slope (b)	T
Calcium	9.63 mg/dl	8.5-10.6	0.21 mg/dl 2.18%	0.57	7.01
Potassium	4.44 mmol/L	3.5-5.5	0.16 mmol/L 3.60%	0.75	10.82
Sodium	140.51 mmol/L	135-148	1.24 mmol/L 0.88%	0.59	6.95
Chloride	103.68 mmol/L	94-110	1.13 mmol/L 1.09%	0.57	9.56
Bicarbonate (CO ₂)	28.56 mmol/L	22-35	1.55 mmol/L 5.43%	0.46	4.12
Glucose	98.07 mg/dl	60-115	13.97 mg/dl 14.24%	1.00	14.61
Urea (BUN)	15.58 mg/dl	7-26	1.99 mg/dl 12.77%	0.67	9.17
Hematocrit	41.78%	33-55	2.62% 6.27% of mean	0.41	5.94
Hemoglobin	14.32 g/dl	12-18	0.89 g/dl 6.22%	0.48	6.45

Table 1. Analytical Results (TAMM)

Notes:

1. An effective measurement is characterized by small average error, a slope approaching 1.0 and a high T-value. The slope is defined as the tangent of the least square fit line of predicted values/actual values.
2. The T-value can be described as a "tracking value" that indicates how well the predicted value tracked with changes in the actual value. It is defined by the slope/standard error of the slope.

Data Sub-set	Hospital	Start Date	Stop Date	Probe Position	Integration Time (milli-sec.)	Sequence Scan	Accepted	Collected
1	Bethesda	6/23/92	7/1/92	Mobile	100	10/10	126	126
2	Bethesda	7/21/92	8/5/92	Mobile	60	10/10	123	124
3	Froedtert	9/09/92	10/23/92	Mobile	60	10/10	118	122
4	Froedtert	10/28/92	12/4/92	Mobile	60	90/90	74	80
5	Froedtert	1/20/93	2/15/93	Fixed	150/250	90/90	73	79

TOTAL 514 531

Table 2. TAMM Database

Appendix I

Subj: Specifications: TAMM Near Infrared Spectrometer for Military Application in the Field (The TAMM Field Instrument) (TAMM Field Prototype)

Date: February 8, 1993

1. General Specifications

1.1 Operating Principle

The TAMM Field Prototype is a near infrared, absorption spectrometric instrument intended to demonstrate the concept of a portable battery-operated instrument for noninvasive blood chemistry analysis in a military field environment. Reflective near infrared absorbance measurements in the human forearm area will provide variable values used in pattern recognition algorithms that determine estimated chemical concentrations of a variety of blood analytes. Light measurements are converted to digital form and processed through pattern recognition algorithms in a computer to provide measurements of 9 blood analytes.

1.2 Spectral Operating Range

1150-1310 nm

1.3 Modes of Operation

1. Diagnostic

- a. measures near infrared light absorption
- b. calculates blood analytes concentrations
- c. displays concentrations (printing optional)

2. Calibration

- a. measures reflectance standard
- b. measures wavelength standard
- c. adjusts instrument calibration

1.4 Analytical Algorithms

1. Genetic neural network analysis (NETGEN)
2. Adaptive signal processing and pattern recognition

1.5 Blood Analvtes

1. Sodium
2. Calcium
3. Chloride
4. Potassium
5. Carbon Dioxide
6. Glucose
7. Urea
8. Hematocrit
9. Hemoglobin

2. Inputs

2.1 Optical

Near infrared reflectance measurements of human forearm.

Dynamic range - Absorbance - 0-1.4 AUs

2.2 Temperature

Contact skin temperature of human forearm in reflectance target area.

2.3 Operator Interface

- a. mode selection
- b. analyte selection
- c. numeric patient identification
- d. other operator inputs

3. Outputs

3.1 Digital Display

3.1.1 Operator prompts

3.1.2 Analyte concentrations

3.2 Printer (Optional Output)

3.2.1 Analyte concentrations and patient information

4. Instrumentation (Hardware)

4.1 Light Source

Light source in the wavelength range of 1150- 1310 nm with performance characteristics suitable for the requirements of 5.0. Irradiance level should not exceed 150 mw/cm².

4.2 Optical Configuration

Light will be transmitted to instrument arm rest. Reflected light will be collected and transmitted back for photodetection, digital conversion and processing. Optics and photodetection will be designed to provide a resolution of 5.0 nm and wavelength stability of ± 2.5 nm.

4.3 Analog-Digital Conversion

Successive approximation converter

14-bit resolution

4.4 Microcomputer

Processing power must be sufficient to perform measurement and analysis within a maximum time period of 20 seconds.

Program and algorithm parameters in EPROM or RAM memory

No hard drive

No diskette "floppy" drive

4.5 Display

40 x 20 liquid crystal display (LCD)

4.6 Power Supplies

As required.

4.7 Temperature Controller

Temperature control should be provided only as required for accurate measurement and only as possible with battery operation.

4.8 Enclosure

A small, compact enclosure that lends itself to being carried on a backpack frame by a Navy Corpsman is desired.

4.9 Power Source Requirements - Battery Operation

Rechargeable battery operation is an absolute requirement of this instrument. Recharge will be accomplished from a separate battery pack. Storage capacity will provide initially for the analysis of a minimum of 10 patients before recharge.

4.10 Weight

The instrument must weigh less than 20 pounds (excluding optional printer).

5. Performance

5.1 Light Measurement Accuracy

Absorbance - ± 0.1 MAU (milliabsorbance units) standard deviation of mean measurement.

5.2 Instrument Accuracy

This instrument will incorporate algorithms developed using the NIR-800 Array Analyzer. Average error, slope and T-value will be consistent with performance on the NIR-800. Algorithm development is not part of this specification.

5.3 Measurement Time

Measurement time will be limited to 10 seconds.

Ken Schlager